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A New Seckel-Like Syndrome of Primordial Dwarfism

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Seckel syndrome is a rare, recessively inherited disorder of severe growth retardation and distinct craniofacial, orodental, and skeletal anomalies. Even though there are well-established minimum diagnostic criteria for this syndrome, controversy exists about its boundaries and criteria for exclusion. We studied 2 remarkably similar, unrelated children with most of the clinical and radiographic manifestations of Seckel's original patient. Although their craniofacial and orodental anomalies are typical of Seckel syndrome, 1 child has unusual appearance of the hands and feet that have not been previously associated with it. This patient appears to define a new Seckel-like syndrome and suggests heterogeneity in this type of primordial dwarfism.

KEY WORDS: Seckel syndrome, primordial dwarfism, craniofacial anomalies, cleft palate, hypodontia, microcephaly, mental retardation, hirsutism, dysharmonic skeletal maturation

INTRODUCTION

In 1960, Seckel drew attention to a heterogeneous group of severely growth-retarded individuals. A subgroup of such patients, now referred to as having the Seckel syndrome, has a distinctive pattern of growth retardation and craniofacial, orodental, and skeletal anomalies similar to those of Seckel's original patient Frances Mil. [Seckel, 1960]. Majewski and Goecke [1982] reviewed 60 reported cases of Seckel syndrome and accepted as authentic only those with proportionate prenatal and postnatal growth retardation (height at least 5 S.D. below the mean), severe microcephaly (both absolute and often relative to stature), moderate to severe mental retardation, prominent nose with a receding forehead, and chin giving rise to the "birdlike" appearance, abnormal ears, highly arched or cleft palate, and relatively large eyes with antimongoloid slant of the palpebral fissures. Although absence of a generalized skeletal dysplasia was important to distinguish it from the osteodysplastic primordial dwarfisms (ODPDs), some skeletal anomalies such as dislocation of radial heads, "hip dysplasia," early closure of the cranial sutures, and retarded bone age with dysharmonic skeletal maturation patterns were included as part of the phenotype. Minor anomalies reported were hirsutism, clinodactyly of 5th fingers, cryptorchidism, clitoromegaly, and enamel hypoplasia of the teeth (Table I). Presence of other major malformations excluded the diagnosis of Seckel syndrome. Thompson and Pembrey [1985] liberalized the diagnostic criteria by including height less than 3 S.D. below the mean, facial asymmetry, small palpebral fissures, telecanthus, microtia, lobeless ears, crowded teeth with malocclusion, and short fingers relative to palm length as part of the phenotype. A characteristic stance with fixed flexion of the hips and knees and dislocation of the knees were also noted. They suggested that the full spectrum of Seckel syndrome was yet to be defined and encouraged reports on additional cases.

We report on 2 unrelated patients, 1 of whom has the classic manifestations of Seckel syndrome. The other child has remarkably similar craniofacial and orodental findings, but her unusual limb malformations suggests that she has a new type of Seckel-like primordial dwarfism. Our attempt to define the boundaries of the Seckel syndrome also allows us to point out the diag-

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TABLE I. Comparison of Clinical Manifestations of Seckel Syndrome* and Our Patients

Findings	n	% Frequency	Patient 1	Patient 2
IUGR and postnatal growth retardation	17/17	100	+	+
Moderate to severe mental retardation	17/17	100	+	+
Microcephaly	17/17	100	+	+
Prominent nasal bridge	17/17	100	+	+
Marked retro/micrognathia	17/17	100	+	+
Clinodactyly of 5th finger	8/8	100	+	+
Severely retarded bone age	12/13	92.3	+	+
Malformed ears	10/12	83.3	+	+
Cryptorchidism in males	3/4	75.0	N/A	N/A
Downslanting palpebral fissures	7/11	63.6	–	+
Proptotic eyes	10/16	62.5	+	+
Hypoplasia of dental enamel	6/10	60.0	–	+
Hip "dysplasia"	5/9	55.6	+	+
Craniosynostosis	7/13	53.8	–	–
Dislocation of radial head	3/6	50.0	+	–
Clitoromegaly in females	3/7	42.9	+	+
Highly arched palate	4/10	40.0	–	–
Hirsutism	3/10	30.0	+	+
Cleft palate	2/17	11.8	+	+

*Modified from Majewski and Goecke [1982].

nostic usefulness of some of its previously underemphasized clinical findings.

CLINICAL REPORTS

Patient 1

A.H. was delivered by repeat caesarean section following spontaneous onset of labor 2 weeks postterm by menstrual dates. She was meconium stained and depressed at birth, with Apgar scores of 1, 4, and 6 at 1, 5, and 10 min, respectively. During intubation, no meconium was noted below her vocal cords. In spite of mild choanal stenosis, micrognathia, microstomia, very small oral cavity, and limited jaw mobility, there was no evidence of glossoptosis and/or respiratory compromise, and she was weaned from the ventilator within 48 hr. Her mother, a 25-year-old, gr3, para1, ab1, woman, was treated for syphilis 3 months before delivery with penicillin, but her pregnancy was otherwise uncomplicated. The patient's birth weight was 1,659 g (mean for 32-week gestation), length was 38.5 cm (mean for 29 wk gestation), and head circumference (OFC) was 32.5 cm (mean for 36-week gestation). When we examined her at age 1 month, her length, weight, and OFC were well below the 5th centile, but the relative macrocephaly noted at birth persisted. She had thick curly scalp hair, narrow hirsute forehead, small palpebral fissures, microstomia, micrognathia, short fingers with proximal interphalangeal joint contractures of fingers 2 and 5, and syndactyly between toes 2/3 and 4/5, bilaterally. Echocardiography, abdominal and head ultrasound, and karyotype (46,XX) were normal. A specific syndrome diagnosis was not established. Following discharge from the nursery with a feeding gastrostomy tube in place, her growth and development proceeded at a slower than expected rate without evidence of regression.

Her father was 25 years old and 155 cm tall; her mother's height was 152 cm. No consanguinity between the parents was admitted, and the family history was otherwise unremarkable.

When last seen at age 34 months, she had severe proportionate dwarfism. Her height (64.5 cm) and OFC (42.2 cm) were at the 50th centile for a 5.5 month old, whereas her weight (4.8 kg) was at the 50th centile for a 1.5 month old. She had a flat forehead, a prominent midface with a beaked nose, and a hypoplastic mandible with severe retromicrognathia. Her eyes were mildly proptotic, with small palpebral fissures (Fig. 1a) measuring 18 mm long (mean for 39-week gestation). Her inner canthal distance of 2.4 cm (mean for 8 months) indicated relative telecanthus when compared with her head circumference. She had hypermetropia and mild bilateral ptosis. Her ears were small, posteriorly angulated, apparently low set, and lobeless (Fig. 1b). She also had a submucous cleft of the soft palate, crowded teeth, class II malocclusion, gemination of the upper right central and lateral incisors, and an absent upper left lateral incisor (Fig. 1c). The remaining age-appropriate teeth were present. There was no clinical evidence of enamel hypoplasia. Clitoromegaly, hypoplastic labia (Fig. 1d), laterally displaced, hypoplastic nipples, mildly webbed neck (Fig. 1a), and generalized mild hirsutism were other clinical findings. She had a distinctive stance (Fig. 2).

Limb malformations included clinodactyly of fingers 2 and 5, brachydactyly of both toes and fingers, most marked in fingers 1 and 5, and camptodactyly of finger 4 (Fig. 3a,b). Her hands were narrow at the wrist, with hypoplastic hypothenar eminences, short digits, abnormal major palmar creases, and single flexion creases on her fifth fingers (Fig. 3c,d). She had cutaneous syndactyly of toes 2/3 and 4/5 and short toes (Fig. 3a). She also had an inability to pronate her forearms bilaterally.

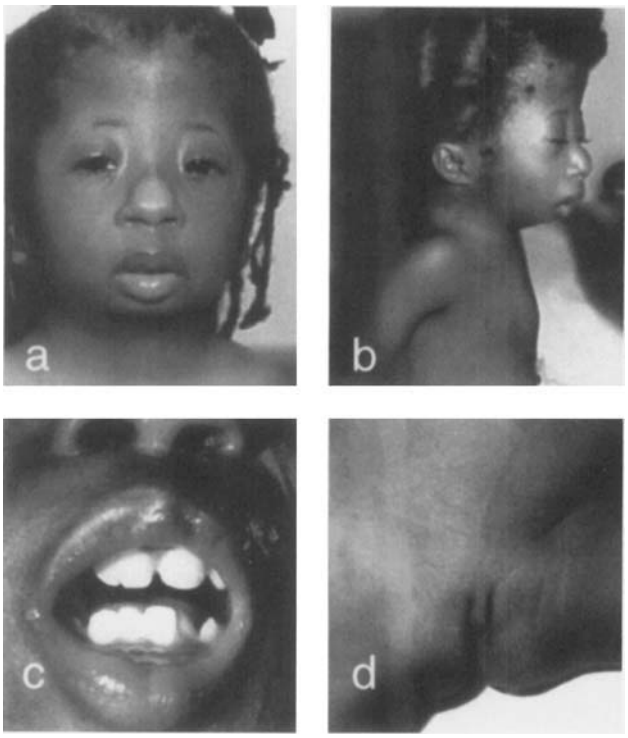

Fig. 1. Major clinical manifestations of the Seckel syndrome in A.H. **a:** Note narrow hirsute forehead, small palpebral fissures with partial ptosis, telecanthus, micrognathia, microstomia, and short neck with mild webbing. **b:** Profile of patient A.H. shows severe retromicrognathia, low-set posteriorly rotated ears, beaklike protrusion of the midface, and mild proptosis. **c:** Note gemination of the lateral and central incisors on upper right and absence of lateral incisor on left. **d:** Hypoplastic labia with prominent clitoris.

Radiographs of her skull, spine, pelvis, chest, and limbs made at 2 years old showed her skeleton to be generally demineralized, with a slender and gracile appearance of the tubular bones. There were multiple growth disturbance lines reflecting periods of cessation of growth, possibly due to feeding difficulties. Her skeletal age was 36–38 weeks of gestation at the knees, <3 months at the wrist, and approximately 16 months at the phalanges. Hand films also showed hypoplastic 1st metacarpals, accessory centers of ossification at the bases of the 2nd and 3rd metacarpals, and coned epiphyses at the bases of the 2nd proximal phalanges. There were congenital anterior dislocations of both radial heads and hypoplasia of the distal clavicles and glenoid fossae. There were 11 rib-bearing "thoracic" vertebrae and 6 non–rib-bearing "lumbar" vertebrae. Her upper thoracic ribs were hypoplastic, more so on the left, with a bell-shaped chest configuration.

The vertebral bodies, particularly those of the lower thoracic spine, were narrow in their anteroposterior dimension, giving them a "tall" configuration. The normal thoracic kyphotic and lumbar lordotic curves of the spine were not well developed, and the patient exhibited a mild mid-thoracic scoliosis convex to the right. The interpediculate spaces of the mid-thoracic spine appeared widened, but there were no other structural vertebral anomalies.

The cranium appeared proportionate to her overall size and had a square shape with a flat frontal bone. There were no signs of premature closure of cranial sutures, increased intracranial pressure, or cerebral hypoplasia. Her face was relatively small, with apparent micrognathia. Both mastoids were underdeveloped and diploic, indicating possible chronic middle ear infection.

The patient's intellectual and adaptive skills were measured by using appropriate sections of the Stanford-Binet Intelligence Scale, Bayley Scales of Infant Development, and the Vineland Adaptive Behavior Scale. She was found to function within the range of mild mental retardation. Receptive language skills were found to be commensurate with cognitive functioning. Expressive language abilities and visual motor integration skills were more significantly delayed than would be expected according to her mental age.

Her thyroid function, complete blood counts, and serum chemistry profile were normal with the exception of a markedly elevated total cholesterol of 235 mg/dL. Growth hormone binding protein (IGFBP3) and insulinlike growth factor I (IGFI) levels were normal.

Patient 2

D.R., a child from the Dominican Republic, described briefly by Pérez-Comas and Salinas [1978], was born of consanguineous parents and had a birth weight of 340 g. At age 2 years, she presented with severe proportionate dwarfism, failure to thrive, mental retardation, microcephaly, cleft of the soft palate, and facial appearance compatible with the Seckel syndrome (Fig. 4). Her weight at age 2 years was 1,816 g (mean for 33-week gestation), her length was 49.5 cm (mean for term newborn), and her OFC was 29.2 cm (mean for 31-week gestation). She had a prominent midface with a relatively large nose, mildly hirsute narrow forehead, sparse scalp hair, proptotic eyes, and small, apparently low-set ears, with hypoplastic ear lobules (Fig. 4). Orodental manifestations included microdontia, hypodontia of the upper and lower lateral incisors (Fig. 5), enamel hypoplasia, a cleft of the soft palate, and retrognathia with a hypoplastic mandible. Her cardiovascular system, thorax, and abdomen were normal. She also had clitoromegaly, hypoplastic labia, and a cutaneous dimple just above the anus. Limb abnormalities included clinodactyly of both 5th fingers, cutaneous syndactyly of toes 2, 3, and 4 bilaterally, and fixed flexion of the hips and knees. Radiographs documented severely retarded bone age, microcephaly, and a relatively small sella turcica. When last seen at age 2 years, she was able to walk and pronounce only a few words (e.g., *Mama* and *Papa*).

Results of laboratory studies including urinary amino acid and mucopoly-saccharide excretion patterns, serum triiodothyronine, thyroxine, thyroid stimulating hormone, plasma cortisol, and 17-hydroxy-

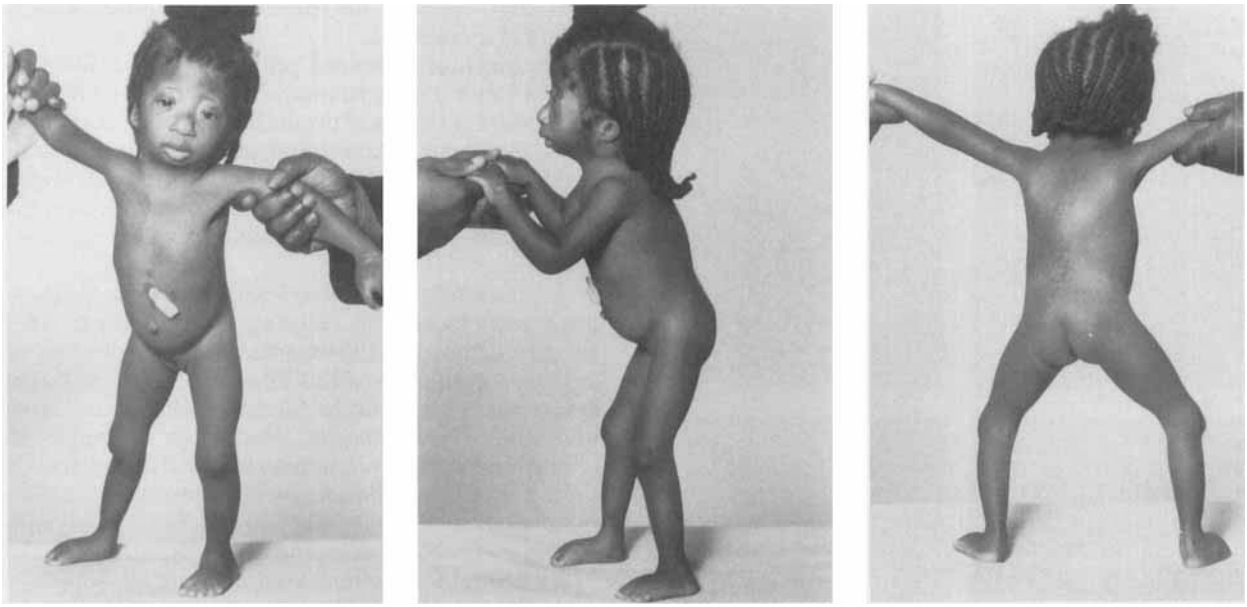

Fig. 2. The unusual stance of patient A.H.

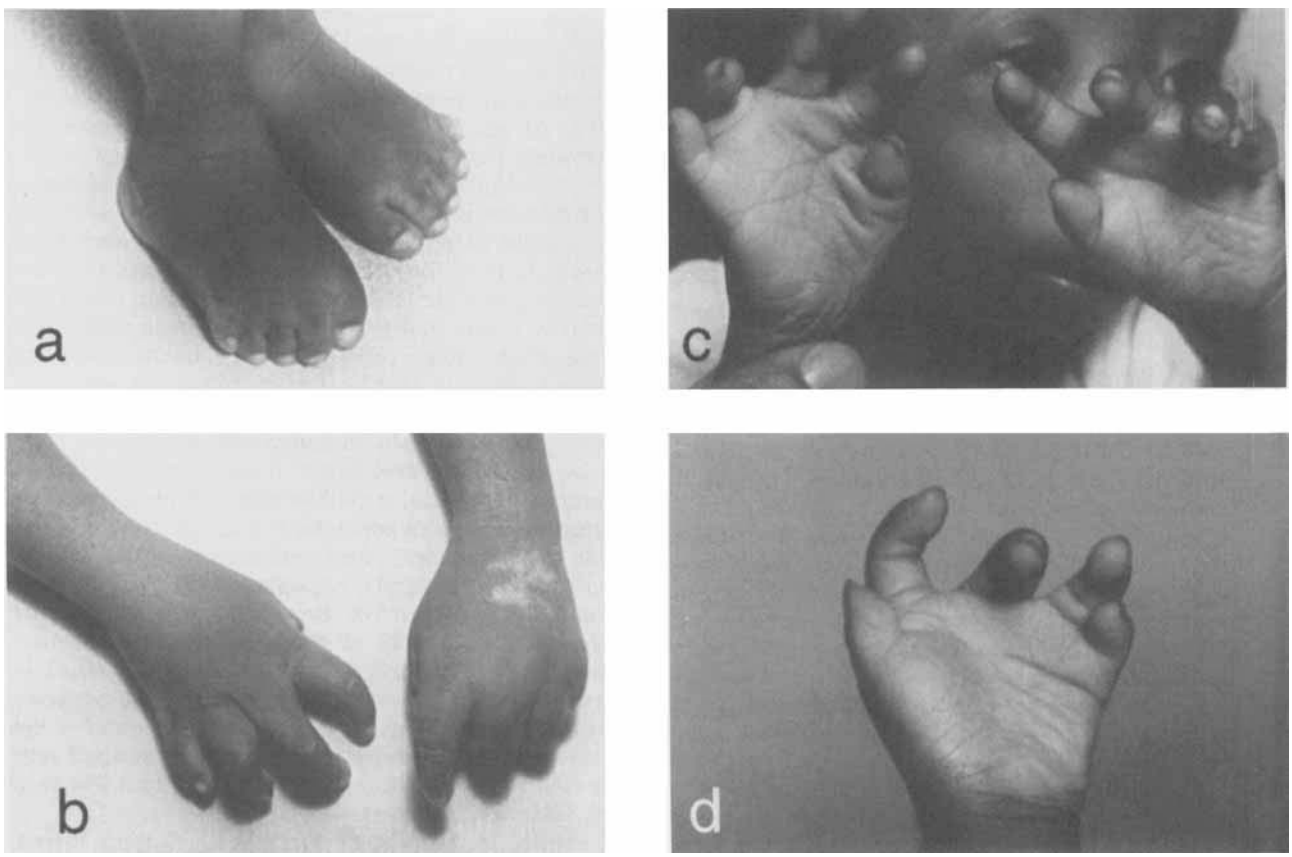

Fig. 3. The limb malformations of patient A.H. that are not usually associated with the Seckel syndrome. Note brachydactyly, clinodactyly of fingers and cutaneous syndactyly of toes (**a,b**), narrow hands with abnormal dermatoglyphics, and hypothenar hypoplasia (**c,d**).

Fig. 4. The facial appearance of D.R. demonstrates the typical manifestations of the Seckel syndrome.

Fig. 5. Study cast of patient D.R. shows hypodontia of upper lateral incisors, generalized microdontia, hypoplastic pitted enamel and midline submucous cleft of the soft palate, and missing lateral incisors.

steroids were all normal. Growth hormone studies (insulin and L-Dopa stimulation tests) gave a paradoxical response, with a high basal level (>20 ng/ml) and a later decline (to 7.5 ng/ml). Metyrapone stimulation test showed an inadequate response, with little increment. Unfortunately, the patient moved out of the country after this evaluation and could not be followed.

DISCUSSION

In 1982, Majewski and Goecke reviewed microcephalic primordial dwarfisms and proposed strict criteria for the diagnosis of Seckel syndrome (Table I). Severe intrauterine and postnatal growth retardation, moderate to severe mental retardation and microcephaly, prominent nasal bridge, marked retromicrognathia, and clinodactyly of the 5th fingers were the only findings present in each of the 17 patients with the syndrome, whereas markedly delayed skeletal maturation was seen in all 12 children on whom data were available. Thus, these were the necessary criteria for the diagnosis of Seckel syndrome, and variability was allowed only in other associated malformations (Table I). Thompson and Pembrey [1985] provided reasons to liberalize this definition to include milder degrees of growth retardation than the arbitrary limit of at least 5 S.D. below the mean, as suggested by Majewski and Goecke [1982]. On this basis, they included the patients of Frijns and Van den Berghe [1976], previously rejected as examples of the Seckel syndrome by Majewski and Goecke [1982]. Microcephaly, absolute as well as relative to the diminutive stature, was required for the diagnosis according to Majewski and Goecke [1982], but not according to Thompson and Pembrey [1985, see case 7, addendum]. In our patient 1, relative macrocephaly was present until age 3 months but not at age 3 years.

Apart from the degree of prenatal and postnatal growth deficit, the most useful clues to the diagnosis of Seckel syndrome are found in the pattern of craniofacial, orodental, and skeletal anomalies. However, most of these manifestations are variable, and some evolve with age, which may make the diagnosis of Seckel syndrome difficult, especially in newborn and older infants. Some of this variability is briefly reviewed in an attempt to define the boundary of the Seckel syndrome.

The outstanding craniofacial anomaly in Seckel syndrome is the prominence of the nasal bridge and septum, beaked curved nose, and the receding forehead that contribute to the "bird-headed" profile. However, these are variable manifestations influenced by age and ethnic and racial backgrounds of the patients. A flat rather than sloping forehead has been documented in at least 3 other accepted cases of Seckel syndrome [Mann and Russell, 1959; Szalay, 1964; Thompson and Pembrey, 1985, case 7]. The nasal bridge was not high in either of our patients, possibly due to their race as was observed in the case reported by Sauk et al. [1973]. Similarly, the eyes in Seckel syndrome have been described as large and proptotic, with antimongoloid

slant or small and widely placed with narrow palpebral fissures and globes disproportionately large for the shallow bony orbits. Both of our patients presented the latter pattern. Hypermetropia, present in 2 of 17 [Black, 1961, cases 1, 2] reported patients was seen in our patient 1. Majewski and Goecke [1982] did not elaborate on the ear abnormalities, simply referring to them as dysplastic. For clarification, the most frequently reported abnormalities were apparently low-set (7/7) and lobeless ears (6/6) [Mann and Russell, 1959; Seckel, 1960, case 1; Szalay, 1964; Harper et al., 1967, cases 1–2; Sauk et al., 1973; Lambotte et al., 1976, case 2] as was seen in both of our patients. Microtia is also frequent.

The importance of orodental manifestations in the diagnosis of Seckel syndrome deserves emphasis. Hypodontia, although not mentioned by Majewski and Goecke [1982, Table III] or by Thompson and Pembrey [1985, table] was present in at least 4 of 17 reported cases [Seckel, 1960, case 1; Szalay, 1964; Harper et al., 1967, cases 1, 2] and in both of our patients. Severe micrognathia with malocclusion and crowding of the teeth, microdontia, macrodontia, and hypoplasia of the enamel have been reported even though their documentation is somewhat sketchy. Both of our patients had small teeth that appeared proportionate to their dental arches and overall body size. Enamel hypoplasia was present only in patient 2. High-arched palate and open or submucous cleft palate, which was present in both of our patients, are less frequently reported, possibly because of the difficulty involved in their detection.

The dysharmonic skeletal maturation in Seckel syndrome follows the pattern usually seen in syndromes with delayed bone age, i.e., the phalangeal ossification centers are more advanced than those of the carpals as seen in our patient 1. However, delayed dental age is a variable finding in Seckel syndrome as normal and delayed patterns of dental eruption are observed with almost equal frequency [Chilvarquer et al., 1987]. Seckel [1960] noted that his first patient had only 11 rib-bearing vertebrae and thus 6 "presacral non–rib-bearing vertebrae," whereas kyphosis or scoliosis was present in at least 4 other accepted cases of the syndrome [Harper et al., 1967, case 2; Sauk et al., 1973; Cervenka et al., 1979, cases 1, 2]. The characteristic stance reported by de la Cruz [1963] was seen in our patient 1 (Fig. 3).

Thus, both of our patients show most of the manifestations of the Seckel syndrome and a remarkable similarity to each other in their craniofacial and orodental findings. However, patient 1 has additional findings not previously associated with the Seckel syndrome. These include macrocephaly relative to body size at birth, mild mental retardation (which may have been present in the patients of Cervenka et al. [1979] and in one of the 2 sibs reported by Frijns and Van den Berghe [1976]), markedly limited jaw mobility, mild webbing of the neck, hand malformation, and brachydactyly and syndactyly of toes. Is this evidence of additional variability in Seckel syndrome or of further heterogeneity in primordial dwarfisms? We favor the latter possibility even though unequivocal evidence for a distinctive new Seckel-like syndrome with malformations of the hand and feet must await description of additional cases.

REFERENCES

Black J (1961): Low birth weight dwarfism. Arch Dis Child 36: 633–644.

Cervenka J, Tsuchiya H, Ishiki T, Suziki M, Mori H (1979): Seckel's dwarfism: Analysis of chromosome breakage and sister chromatid exchanges. Am J Dis Child 133:555–556.

Chilvarquer LW, dos Santos VIM, dos Santos e Silva MG, Young RS, Jorgenson RJ, Arena JFP (1987): Orofacial manifestations of the Seckel syndrome. J Dent Child 54:129–131.

de la Cruz F (1963): Bird-headed dwarf: A case report. Am J Mental Deficien 68:54–62.

Frijns JP, Van den Berghe H (1976): Familial bird headed dwarfism. Acta Paediatr Belg 29:121–122.

Harper RG, Orti E, Baker RK (1967): Bird headed dwarfs (Seckel's syndrome). J Pediatr 70:799–804.

Lambotte C, Dony G, Bonnet F (1976): Seckel syndrome–birdheaded dwarfism. Acta Paediatr Belg 29:79–82.

Majewski F, Goecke T (1982): Studies of microcephalic primordial dwarfism I: Approach to a delineation of the Seckel syndrome. Am J Med Genet 12:7–21.

Mann TB, Russell A (1959): A study of microcephalic midget of extreme type. Proc R Soc Med 52:1024–1027.

Peréz-Comas A, Salinas CF (1978): Seckel syndrome in a Latinoamerican patient. Proceedings of 1978 Birth Defects Conference, San Francisco.

Sauk JJ, Litt R, Espiritu CE, Delaney JR (1973): Familial bird-headed dwarfism (Seckel's syndrome). J Med Genet 10:196–198.

Seckel HPG (1960): "Bird Headed Dwarfs." Springfield, IL: CC Thomas.

Szalay GC (1964): Intrauterine growth retardation versus Silver's syndrome. J Pediatr 64:234–240.

Thompson E, Pembrey M (1985): Seckel syndrome: An overdiagnosed syndrome. J Med Genet 22:192–201.